

PATENT
Attorney Docket No. EURA-004/00US
(Formerly 451194-101)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gopi M. Venkatesh et al.

Application No.: 10/713,929

Confirmation No.: 4820

Filed: November 14, 2003

Group Art Unit: 1615

For: MODIFIED RELEASE DOSAGE FORMS OF
SKELETAL MUSCLE RELAXANTS

Examiner: BARHAM, Bethany P.

DECLARATION UNDER 37 C.F.R. § 1.131

I, Dr. Gopi Venkatesh declare as follows:

1. I am a named inventor of the above-noted application (Ser. No. 10/713,929)
2. I have read and understood the Official Action of January 11, 2008, and in particular the rejection of the pending claims under 35 U.S.C. §103 over the combination of U.S. Publ. No. 2004/0197407 (the '407 application) and U.S. Publ. Nos. 2003/0215496 or 2003/0099711.
3. I understand that the earliest asserted priority date of the '407 application is February 11, 2003, through the priority claim to U.S. Provisional Application Ser. No. 60/446,425.
4. The subject matter of the pending claims of the present application was invented by Gopi Venkatesh and James M. Clevenger (the named inventors) prior to February 11, 2003.
5. Example 3 of the instant application describes the formulation and production of a multiparticulate dosage form of cyclobenzaprine, wherein the cyclobenzaprine is coated on sugar spheres and covered with a water insoluble polymer to produce extended release beads (see paragraph 0045). Figure 4 of the instant application shows the release rate of the finished beads of Example 3 (e.g., **Batch 805-AAA-105**).

6. Exhibit A, dated before February 11, 2003, shows a "Master Formula" sheet documenting the production of the intermediate cyclobenzaprine coated beads used to make **Batch 805-AAA-105**. This intermediate batch (designated **Lot No. 837-AG-034**) comprises:

- "Sugar Spheres" (5475 g) coated with "cyclobenzaprine HCl" (1875 g) from "Acetone, NF 50/50% Ratio" and "USP Purified Water, 50/50% Ratio";
- seal coated with "2.00%" of "Opadry Clear YS-1-7006".

Exhibit B, dated before February 11, 2003, shows a "Master Formula" sheet documenting the actual production of **Batch 805-AAA-105** by coating the intermediate cyclobenzaprine beads of **Lot No. 837-AG-034** with an extended release water insoluble polymer:

- ER coating of **Lot No. 837-AG-034** with "Ethylcellulose 10P Premium (10 cps)" (363.6 g) and "Diethyl Phthalate" (36.4 g) dissolved in "Acetone, NF (98 parts)" and "USP Purified Water (2 parts)". Samples were collected with a coating weight of "10%" (designated **Batch or Lot No. 805-AAA-105**).

Exhibit C, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for "Lot # 805-AAA-105-10" (i.e., 10 wt.% ER coating, Batch 805-AAA-105). The data are identical to that presented in graphical form for the sample designated "10% ER Coating Wt., Batch 805AAA105" in Figure 4 of the instant application and shows that the 10% ER coated beads exhibit a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

7. Exhibit D, dated before February 11, 2003, is a batch record showing the ingredients of "Cyclobenzaprine HCl ER Beads", **Lot No. PE271EA001**:

- “Cyclobenzaprine HCl Intermediate Beads”, Item code **PE249**; coated with “Ethylcellulose” and “Diethyl Phthalate”.

Exhibit E, dated before February 11, 2003, documents the manufacture of “Cyclobenzaprine HCl MR Capsules, 30 mg”, **Lot No. PF306EA001**:

- “White, Opaque Hard Gelatin Capsules, Size 4”, filled with “Cyclobenzaprine HCl Extended Release Beads”, Item code **PE271**.

Exhibit F, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for clinical batch “Lot # PF306EA001”. The data are identical to that presented in graphical form for the clinical sample designated “PF306EA001” in Figure 6, Examples 4 and 5 of the instant application. Formulation PF306EA001 shows a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

8. Thus, Exhibits A and B document the production of the identical multi-particulate cyclobenzaprine dosage forms described in Example 3 of the present application, and as set forth in the instant claims, before February 11, 2003.

9. Thus, Exhibits D and E document the production of the identical clinical batch described in Examples 4 and 5 of the present application, and as set forth in the instant claims, before February 11, 2003.

10. I further declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that

such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Respectfully submitted,

Gopi Venkatesh

Gopi Venkatesh

1/30/08

Date

Master Formula

Page _____ of _____

Product Name: Cyclobenzaprine HCl, Drug Layered Beads		Batch Number: 837A6094		Batch Size: 7500.0 grams		Date: _____	
Physical Description: Off White		Capsule Size: N/A		Label (mg \ Unit): N/A		Unit Weight (mg): N/A	
Imprint (Uppers): N \ A		Imprint (Lowers): N \ A		Reviewed By: <i>A. Gallo</i> <i>Orlando</i>		Written By: A. Gallo <i>Orlando</i>	
ITEM #	Ingredients (Trade Name Grade)	Raw Material Lot #	Quantity %	Mgt. Unit	Gms/batch	Quantity	Weighted
1	*Cyclobenzaprine HCl	C14607401	25.00	7.50	1875.0 gm	1875.0	1875.0
2	Sugar Spheres 20 - 25 Mesh (Hansen)	RD - 991114	73.00	21.90	5475.0 gm	4750.0	4750.0
3	**Opadry Clear YS - 1 - 7006	H10507376	2.00	0.60	150.0 gm	150.0	150.0
4							
5							
6							
7							
8							
9							
10	Acetone, NF 50/50 % Ratio	A10707332			2812.50 ml	2812.50	2812.50
11	USP Purified Water, 50/50 % Ratio	W-10002061B			2812.50 ml	2812.50	2812.50
12	USP Purified Water @ 10.0 % of Seal Coat	W-10002061B			1350.0 ml	1350.0	1350.0
Total:			100.00	30.00	7500.0 gm	7500.0	7500.0
Objective: to evaluate dose @ 25.0 % Using GPCG 5							

* Item #10, 11, 12 is use to make coating solutions. Both mg unit and g batch totals do not reflect entries.

Note: Acetone, NF / USP Purified Water 50/50 Ratio.

Exhibit B

Project No.:

Book No. 805

TITLE CYCLOBENZAPRINE HCl EC BEADS.

From Page No 104

Purpose: To EC coat Cyclobenzaprine HCl drug layered beads using solvent (50:50) Acetone : H₂O as a media. The drug layered beads were then Ethyl Cellulosic coated using Acetone : H₂O (98:2). The EC was done using Gilett GPCG-5 Wurster.

Master Formula

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Product Name: Cyclobenzaprine HCl – Extended Release Beads (25.0 mg)

Physical Description : Extended Release Coating

Lot # 805-AAA-105

Date: 4

Total:

Objective: Evaluating Dose @ 10.0 % Samples were taken @ 7, 8, 9, & 10% of EC applied.

To Page No

Witnessed & Understood by me.

Date

Invented by

Anthony A. Arpaio

Date

ISSUED BY Q.A.

Eurand America, Inc.

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Cyclobenzaprine HCl MR Capsules, 30 mg
Batch Size - 130,000 Capsules (Theoretical))
MF#: A-60PF306-A

Lot # PF306EA	001	Date of Manufacturing:	[REDACTED]
Effective Date:	[REDACTED]		
Prepared By:	[Signature]	Date:	[REDACTED]
MFG. Approval By:	[Signature]	Date:	[REDACTED]
R&D Approval By:	[Signature]	Date:	[REDACTED]
QA Approval By:	[Signature]	Date:	[REDACTED]
QA Issue:	[Signature]	Date:	[REDACTED]
QA Audited By:	[Signature]	Date:	[REDACTED]

BATCH INGREDIENTS					
Item Code	Item No.	mg per capsule	% per Capsule (w/w)	Ingredient Name	Quantity per Batch
G134	1	37.00 ¹	21.91	White, Opaque Hard Gelatin Capsules, Size 4,	4.81 kg
PE271	2	131.87 ²	78.09	Cyclobenzaprine HCl Extended Release Beads	17.14kg
	Total	168.87			21.95 kg

¹Based on a theoretical empty capsule weight of 37.0 mg

²Equivalent to 30 mg of Cyclobenzaprine Hydrochloride (Beads based on a theoretical assay of 22.75%)

ISSUED BY Q.A.

Eurand America, Inc.
 Cyclobenzaprine HCl ER Beads
 Batch Size: 85 kg (Theoretical)
 MF #: A-50PE271-A

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Lot #: PE271EA 001	Date of Manufacturing: [REDACTED]
Effective Date: [REDACTED]	
Prepared By: [Signature]	Date: [REDACTED]
Mfg. Approval By: [Signature]	Date: [REDACTED]
R&D Approval By: [Signature]	Date: [REDACTED]
QA Approval By: [Signature]	Date: [REDACTED]
QA Issue: [Signature]	Date: [REDACTED]
QA Audited By: [Signature]	Date: [REDACTED]

Item No.	Item Code	Bead Dosage (mg/g)	% per Batch (w/w)	Ingredient Name	Theoretical Quantity Per Batch**
1	PE249	910.00	91.00	Cyclobenzaprine HCl Intermediate Beads	77.4 Kg
2	E114	81.25	8.13	Ethylcellulose, Premium Std 10cps	6.9 Kg
3	D118	8.75	0.88	Diethyl Phthalate, NF	0.75 Kg
4	A107	---	---	Acetone, NF*	116.7 Kg
5	W100	---	---	Purified Water, USP*	2.4 Kg
		1000.00	100.01	TOTAL=	85.0 Kg

*Removed from process during the drying process

**Actual batch is based on the actual quantity of the Intermediate Beads available for use. See page 2

Exhibit F

**Cyclobenzaprine 30mg MR Capsules
Lot# PF306EA001**

1 hour				Avg. STD		8 hour				Avg. STD	
CHKSTD	262100	CHKSTD	256775	259438	259438	CHKSTD	283363	CHKSTD	270750	CHKSTD	267053
1	10845	7	14041			1	205685	7	220886		
2	5836	8	14416			2	215916	8	218836		
3	12708	9	0			3	218018	9	205793		
4	11645	10	14435			4	211804	10	219400		
5	11232	11	15293			5	220533	11	211189		
6	10460	12	13404			6	214893	12	222248		
CHKSTD	256775	CHKSTD	262386	259581		CHKSTD	270750	CHKSTD	263356	CHKSTD	267053
2 hour				12 hour				24 hour			
CHKSTD	262386	CHKSTD	283589	262988	CHKSTD	283356	CHKSTD	281737	CHKSTD	262547	CHKSTD
1	73230	7	63080			1	232004	7	247658		
2	80450	8	86176			2	245230	8	245567		
3	80522	9	81274			3	246103	9	230755		
4	77577	10	84345			4	245046	10	248980		
5	81204	11	78231			5	251569	11	237970		
6	80205	12	85540			6	244480	12	252555		
CHKSTD	263589	CHKSTD	262191	262890		CHKSTD	281737	CHKSTD	281580	CHKSTD	281864
4 hour				16 hour				48 hour			
CHKSTD	262191	CHKSTD	261515	281853	CHKSTD	281590	CHKSTD	281252	CHKSTD	281421	CHKSTD
1	135093	7	159205			1	247344	7	284019		
2	143494	8	158288			2	282134	8	282718		
3	145159	9	151618			3	283893	9	242544		
4	143021	10	159810			4	258831	10	285913		
5	149228	11	149087			5	288488	11	254622		
6	145149	12	160801			6	285056	12	268862		
CHKSTD	281515	CHKSTD	288598	285057		CHKSTD	261252	CHKSTD	282478	CHKSTD	281864
8 hour				STD conc				mg/ml			
CHKSTD	288598	CHKSTD	288252	287425				Strength	30	mg	
1	182176	7	197178								
2	191272	8	194590								
3	192435	9	186135								
4	187095	10	197029								
5	198802	11	186727								
6	190502	12	198923								
CHKSTD	286252	CHKSTD	283363	264808							
1 hour (FIO)				8 hour (80 - 90%)				48 hour (NLT 75%)			
1	4	7	5	1	60	7	75				
2	2	8	5	2	73	8	74				
3	4	9	0	3	73	9	70				
4	4	10	5	4	72	10	74				
5	4	11	5	5	74	11	71				
6	4	12	5	6	73	12	75				
Average:	4	%		Average:	73	%		Average:	84	%	Pass
2 hour (9 - 40%)				12 hour (FIO)				48 hour (NLT 75%)			
1	25	7	28	1	80	7	85				
2	28	8	30	2	84	8	85				
3	28	9	28	3	85	9	80				
4	27	10	29	4	84	10	86				
5	28	11	27	5	86	11	82				
6	28	12	29	6	84	12	87				
Average:	28	%		Average:	84	%		Average:	84	%	Pass
4 hour (30 - 60%)				16 hour (NLT 75%)				48 hour (NLT 75%)			
1	47	7	54	1	85	7	91				
2	49	8	54	2	80	8	81				
3	50	9	52	3	91	9	84				
4	49	10	54	4	89	10	92				
5	51	11	51	5	93	11	88				
6	50	12	55	6	91	12	93				
Average:	51	%		Average:	80	%		Average:	80	%	Pass
8 hour (FIO)				12 hour (FIO)				48 hour (NLT 75%)			
1	61	7	67	1	80	7	85				
2	65	8	66	2	84	8	85				
3	65	9	63	3	85	9	80				
4	63	10	67	4	89	10	92				
5	67	11	64	5	93	11	88				
6	64	12	68	6	91	12	93				
Average:	65	%		Average:	80	%		Average:	80	%	Pass